REMARKS

Reconsideration and withdrawal of the rejections of the February 7, 2003 Office Action are respectfully requested in view of the amendments, remarks and enclosures herewith.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 1-56 are pending, and claims 1-3, 18, 21, 24, 25, 30, 31, 34-36, 45 and 56 are under examination. Claims 1-3, 18, 21, 24, 25, 30, 34-36, 45 and 56 have been amended, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is respectfully submitted that the claims, as originally presented and as amended herein, are patentably distinct over the art, and that those claims are and were in full compliance with the requirements of 35 U.S.C. 112. The amendments and the remarks made herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§101, 102, 103 or 112. Rather, the amendments and remarks herewith are made simply for clarification and to round out the scope of protection to which Applicant is entitled.

II. THE OBJECTIONS TO THE SPECIFICATION ARE OVERCOME

The specification was objected to because of the use of a trademark on page 22 of the specification. The objection is respectfully traversed. The specification has been amended to capitalize the trademark 'CARBOPOL®' such that it is believed the specification is now in compliance with the guidelines for the use of trademarks in patent applications. Consequently, reconsideration and withdrawal of the objection is respectfully requested.

The specification was also objected to due to the use of "combo" and "*crypto*" on page 40 of the application. The objection is respectfully traversed.The amendment herein replaces these terms with "combination" and "*Cryptosporidium*", respectively. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Additionally, the specification was objected to due to the presence of numbered paragraphs on pages 43 to 48 of the specification. The objection is respectfully traversed. The Office Action states that the paragraphs "appear to be the same as the claims of pages 53-57 of

the specification. Claims should be designated as claims and not paragraphs." Office Action at 3.

It is respectfully submitted that the paragraphs on pages 43 to 48 are not identical to the claims on pages 53 to 57. The numbered paragraphs are included in the present application to more accurately describe all the features and embodiments of the present invention, some of which may not be included in the claims due to the conventions of U.S. claim construction. Since numbered paragraphs are not prohibited by any of the MPEP, 35 U.S.C. or 37 C.F.R., it is respectfully requested that the objection to the specification based on the numbered paragraphs be reconsidered and withdrawn.

III. THE REJCTIONS UNDER 35 U.S.C. §112 ARE OVERCOME

Claims 1-3, 18, 21, 24-25, 30-31, 34-36, 45 and 56 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while enabled for a vaccine comprising a P21 antigen and a Cp15/60 antigen, allegedly is not enabled for a vaccine comprising epitopes of a P21 antigen and epitopes of a Cp 15/60 antigen. The rejection is respectfully traversed. Initially, it is pointed out that the Office Action repeatedly refers to "Cp 15/16" instead of Cp 15/60. This has been corrected throughout the present response, with the exception of direct quotations from the Office Action, wherein the error is noted as such.

The Office Action alleges that "[t]he specification does not disclose any specific structural information about the epitopes or fragments of the P21 or Cp 15/16 [sic] antigens." Office Action at 4. Further, it is alleged that one of skill in the art would not be able to make and use the invention commensurate in scope with the present claims without undue expermentation.

It is respectfully submitted that the assertion in the Office Action that undue experimentation is required to practice the instantly claimed invention is inaccurate. The Examiner is respectfully directed to *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), wherein the Federal Circuit stated at 1404 that:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the

> invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted].

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing the factors summarized in *In re Wands*. These factors include, for example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims; all of which must be taken into account.

Applying the law to the instant facts, it is clear that enablement exists. To this end, it is respectfully submitted that the specification provides one of ordinary skill in the art with sufficient guidance to make and use the present invention; see, for example, the specification at page 29, lines 18-22:

> A preferred method to obtain antigens or epitopes of interest is to clone the DNA sequence encoding the antigen or epitope of interest into a fusion or non-fusion plasmid and to have its expression in E. coli. Fusion plasmids (e.g., that express the antigen(s) or epitope(s) with a tag such as a His tag) are preferred as they allows [sic] one to recover easily the produced antigen.

Applicants' invention is clearly enabled because a skilled artisan would readily understand that standard techniques for identifying epitopes can be used to characterize epitopes of P21 and CP 15/60. Predictability in the art did exist at the time of filing and, coupled with the knowledge of one of ordinary skill in the art and the guidance of the present application, there is sufficient evidence that Applicants' disclosure does satisfy the enablement requirement.

One of ordinary skill in the art would be readily aware that epitopes are a cluster of amino acid residues that bind specifically to the binding site of an immunogobulin molecule. The most commonly used method for localizing protein epitopes consists of identifying which peptide fragments of the antigen are able to cross-react with antibodies raised against the intact protein. Such an artisan would appreciate that there are a number of highly efficient methods of identifying such epitopes, including the pepscan technique described in Geysen et al. (J. Mol.

Recogn. 1988, 1:32-41), the use of synthetic peptides, and analysis of the protein through use of structural parameters such as accessibility, segmental mobility and hydrophobicity (*See* Hopp, T. Method Enzymol. 1989, 178:571-585, or Van Regenmortel, J. J. Pelleque Peptide Res. 1994, 7:224-228). All of the mentioned techniques are well known to those of ordinary skill in the art, and are considered routine testing, such that use of these techniques would not be undue experimentation.

In short, no undue experimentation would be necessary, sufficient direction and guidance are presented in the specification, the prior art provides sufficient examples and guidance for characterizing such epitopes, and the relative skill of those in the art is high, such that the claims are sufficiently enabled for a vaccine comprising epitopes of a P21 antigen and epitopes of a Cp 15/60 antigen. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Additionally, claim 45 was rejected under 35 U.S.C. §112, second paragraph, as allegedly unclear due to use of the term "optionally." Specifically, the Office Action asks whether the instructions are included in the kit. The rejection is respectfully traversed.

The use of the term "optionally" in claims is not new. The term is afforded its natural meaning, such that an item optionally included in a kit may be included in the kit, although the kit does not require inclusion of the item. Claim 45 utilizes the term "optionally" in accordance with its standard definition, such that the claimed kit may include directions for admixture or administration, but does not have to. Applicants respectfully suggest that the term "optionally" is used in a clear manner consistent with its accepted definition, such that claim 45 does not require amendment to clarify. Consequently, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

IV. THE ART REJECTIONS ARE OVERCOME

Claims 1-3, 18, 21, 24-25, 30-31, 34-36, 45 and 56 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Perryman *et al.* (International Application Publication No. WO 98/07320), in view of Jenkins *et al.* (U.S. Patent No. 5,591,434). The rejection is respectfully traversed.

The cited documents do not render obvious the instant invention.

Further, it is well-settled that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further still, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the Section 103 rejection to be proper, **both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure**. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

The Office Action alleges that it would have been obvious to combine the Cp15/60 vaccine composition of Jenkins *et al.* to the vaccine formulations of Perryman *et al.* because Perryman *et al.* "teach that the vaccine formulations may include combinations of appropriate antigens." Office Action at 8. It is respectfully asserted that Perryman *et al.* does not define what features make an antigen "appropriate." In fact, Perryman *et al.* provides no guidance as to what antigens may be used in combination with the invention; nor does Perryman *et al.* provide guidance as to specific features that one may use to evaluate the "appropriateness" of an additional antigen. In contrast, the present invention excludes the use of antigens which would be inappropriate, (e.g., would cause "efficacy interference," see below), by the use of the phrase "consisting essentially of" in the claims.

Additionally, Jenkins *et al.* does not discuss the possibility of CP15/60 being included with additional antigens in a vaccine.

One of skill in the art, reading Perryman *et al.* and Jenkins *et al.* would not have been motivated to combine CP15/60 and P21. Simply, neither Perryman *et al.* nor Jenkins *et al.* provide any teachings or guidance regarding such a combination. And, neither Perryman *et al.* nor Jenkins *et al.* provide any expectation of success resulting from such a combination, especially in view of "efficacy interference," a phenomenon any individual of skill in the art would be aware of. In fact, "efficacy interference" is one of the problems associated with immunology the present invention overcomes, as seen in the discussion of "efficacy interference" at page 4 of the present application.

Simply, "efficacy interference" is a well known problem in the art that relates especially to multivalent compositions, such as those comprising multiple antigens. "Efficacy interference" is a failure of one or more antigens in a combination composition to maintain or achieve efficacy. This phenomenon is believed to be caused by interference by that antigen stimulating an immunological, antigenic, antibody, or protective response in the host when administered, because of the presence of the other antigens. For instance, rabies antigens in a combination with other antigens suffer interference from or interfere with the stimulation of an immunological, antigenic, antibody or protective response by those other antigens in such a composition, especially when that composition is administered to dogs. More particularly, antigens, such as rabies antigens and Leptospira antigens, when administered with one or more other antigens can interfere with the response elicited by those antigens.

"Efficacy interference" can preclude the development of some vaccines because it cannot be predicted whether a given set of antigens will function in harmony in a vaccine or whether they will interfere with each other. For example, particularly in the U.S. a rabies combination or multivalent or "cocktail" vaccine or immunological composition, is not presently available due to the inability of any previous combinations to pass efficacy testing. Such prior combinations exhibit "efficacy interference."

For additional information regarding efficacy interference, the Examiner is invited to review U.S. Patent Nos. 5,843,456 (also referenced in the specification at page 4), and 6,368,603, and Pines *et al.*, Vaccine 1999, 17(13-14):1650-6 (abstract enclosed).

Accordingly, Perryman et al. and Jenkins et al. provide no motivation to combine their teachings, nor do they provide any expectation of success resulting from such a combination, especially in view of considerations including, but not limited to, "efficacy interference". Consequently, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) are respectfully requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to further examination and/or allowance, an interview with the is respectfully requested, prior to issuance of any paper other than a first Office Action on the merits and/or a Notice of Allowance; and, the Examiner is respectfully

requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks and amendments herewith and those of record, the application is in condition for allowance. Favorable reconsideration of the rejections of the application and prompt issuance of a Notice of Allowance, or an interview at a very early date with a view to placing the application in condition for allowance, are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date.

Respectfully submitted,

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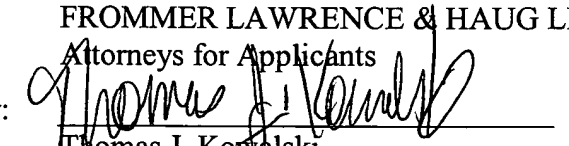
By: 

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Vaccine. 1999 Mar 26;17(13-14):1650-6. Related Articles, Links

New acellular pertussis-containing paediatric combined vaccines.

Pines E, Barrand M, Fabre P, Salomon H, Blondeau C, Wood SC, Hoffenbach A.

Pasteur Merieux Connaught, Marnes-la Coquette, France.

Combined pediatric vaccines have the advantages of conferring protection against multiple common infectious diseases with a reduced number of injections. Their use should lead to better compliance to recommended vaccination schedules. Diphtheria (D), tetanus (T) and whole-cell pertussis vaccine (P) have been successfully combined, with or without inactivated poliovirus vaccine (IPV) in the same syringe for many years. Recently developed acellular pertussis (aP) Haemophilus influenzae type B (Hib), inactivated poliomyelitis virus and hepatitis B vaccines are ideal candidates for inclusion in current combined vaccines. Nevertheless, the development of new combinations has to face preclinical and clinical issues: the appropriate formulation of the new antigen(s) and other vaccine components needs to be determined to ensure compatibility and guard against potential additive or unexpected adverse reactions; potential immunological interference between antigens and the negative impact of other vaccine components on immunogenicity may occur, and these have to be examined also. Whole-cell pertussis vaccines are highly protective against whooping cough, but the severe adverse reactions that these vaccines sometimes produce have led to hesitation over their use, including the decision of some countries to stop pertussis immunization. To increase the acceptability of pertussis vaccination, Pasteur Merieux Connaught has developed a combined D, T and a two-component acellular pertussis vaccine (DTaP), composed of purified pertussis toxoid (PT) and filamentous haemagglutinin (FHA), which has been shown to be effective in an efficacy trial conducted in Senegal. Acellular DTaP vaccines are immunogenic and have a better safety profile than DTP vaccines, when given either for the primary series, for the booster vaccination or for both. In order to meet worldwide demands, the combined DTaP-IPV or DTP-IPV has been developed for countries where IPV is recommended. Following the encouragement of the WHO, an H. influenzae type B tetanus-conjugated (Act-HIB) vaccine, has been combined in a full liquid formulation with the whole-cell DTP. This vaccine showed a good safety and immunogenicity profile in infants and in toddlers. A combined DTaP-IPV-PRP-T vaccine (where the Act-HIB vaccine is reconstituted by the full-liquid DTaP-IPV) also has been successfully developed both for the primary series and for booster vaccination; although, a reduced immunogenicity against PRP observed after the primary series, this did not affect vaccine priming. Hepatitis B immunization campaigns targeting high-risk groups have failed to control the disease in areas of low endemicity. In 1992, the WHO recommended that hepatitis B vaccination should be integrated into the EPI in all countries by 1997-1999. For that purpose, hepatitis B vaccine is currently evaluated in pediatric combined vaccines. Developing new combination vaccines is a difficult but essential process for maintaining high immunization rates worldwide against infectious diseases, provided that the costs are acceptable. New combined vaccines including pneumococcal and meningococcal component are under wide-scale development.

Publication Types:
- Review
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